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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/588,553	06/07/00	FREYSSINET J	P101614-0000

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EXAMINER	
GRUN, J	
ART UNIT	**PAPER NUMBER**
1641	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/588,553	Applicant(s) FREYSSINET et al.
	Examiner James L. Grun, Ph.D.	Group Art Unit 1641

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *36-63* is/are pending in the application.

Of the above, claim(s) *45-63* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *36-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) *08/750,776*.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. When formal drawings are submitted, the draftsperson will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch at (703) 305-8404.

Applicant's election with traverse of Group I, claims 36-44, in Paper No. 5 is acknowledged. The traversal is on the ground(s) that a complete search for the Group I claims would inherently encompass a search for the subject matter of Group II and therefore a search of these two groups together would not be burdensome. This is not found persuasive because, although the searches of the two groups may overlap, they are clearly not co-extensive. The use of a second receptor to identify a particular subgroup clearly requires a different search than an enzymatic determination.

The requirement is still deemed proper and is therefore made FINAL.

Claims 45-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-44 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 36-40 and 42-44, the interrelationships of the member and the receptor to the solid phase are not clear.

Claims 36-44, as method claims, should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim. It is not clear how determining complex relates to determining an amount or presence of a member.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-37, 39-40, and 42-44 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Thiagarajan et al (J. Biol. Chem. 266: 24302-24307, 1991).

Thiagarajan et al bound purified annexin V to resting and agonist-activated platelets and platelet-derived microparticles, considered herein solid phases, and determined the binding of the

protein by a number of methods, including radiobinding assay (e.g. Figs. 1 or 6), flow cytometry (e.g. Fig. 7), and inhibition of prothrombinase activity (e.g. page 24303, bottom of col. 1, and Fig. 2).

Claims 36 and 37 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Rote et al (Clin. Immunol. Immunopathol. 66: 193-200, 1993).

Rote et al bound anti-phospholipid antibodies to resting and activated platelets, considered herein a solid phase, and determined the binding of the antibodies to their antigens on the platelets.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 36-38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al (Thrombosis and Haemostasis 65: 467-473, 1991) in view of Rote et al (Clin. Immunol. Immunopathol. 66: 193-200, 1993) and Margel et al (J. Cell Sci. 56: 157-175, 1982).

Claims 36-38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al (Thrombosis and Haemostasis 65: 467-473, 1991) in view of Rote et al (Clin. Immunol. Immunopathol. 66: 193-200, 1993) and Carriere (AU 22948/88).

Claims 36-38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al (Thrombosis and Haemostasis 65: 467-473, 1991), in view of Rote et al (Clin. Immunol. Immunopathol. 66: 193-200, 1993), and further in view of Hajek et al (U.S. 5,340,719) and/or Harlow et al.

Abrams et al (Thrombosis and Haemostasis 65: 467-473, 1991) teach flow cytometry for the detection of activated platelets and platelet-derived microparticles. The reference teaches the variety of markers and antibodies known to the art at that time for the detection (e.g. page 468, Table 1). Further, Abrams et al teach re-orientation of phosphatidylserine in activated platelet membranes as an activation-dependent marker. Detection of the simultaneous binding of two antibodies is taught, such as binding of platelets with antibodies specific for activation dependent and independent markers (e.g. page 469). Also taught is the conventional use of biotin-avidin bridges for indirect labelling (e.g. page 469). In contrast to the invention as instantly claimed, the reference does not teach antibodies for the detection of phosphatidylserine in activated platelet membranes, use of a solid phase such as particulate labels, nor alternatives to flow cytometry.

As set forth above, Rote et al teach antibodies for the detection of phosphatidylserine in activated platelet membranes by flow cytometry.

Margel et al teach particulate labels for cell labelling, including fluorescently labelled particles for use in detection by microscopy or flow cytometry. Direct or indirect labelling is taught (e.g. page 164, Fig. 5).

Carriere (AU 22948/88) discloses a method for the determination of a cell population (defined (page 7) as an animal cell, such as platelets, human cell, protozoan cell, or microorganism) or subpopulation therein via the determination of their cell-surface antigens in which a cell population is contacted with a solid-phase immobilized separation reagent for the specific positive immunocapture of target cells and a specific labelled detection reagent (entire document, particularly: pages 6-7, 9-10, and 22-23; and, Claims). The reference teaches that sequential separation and labelling of cells was known to the art (e.g. pages 21-22), but that simultaneous separation and labelling is preferred. In the simultaneous method preferred by the reference, the cells bound to the separation reagent, a proportion of which are labelled by also having bound detection reagent, are separated from unbound cells and detection reagent, and the number of positively separated labelled cells are determined as directly proportional to the measurement of label (pages 11 and 19-20). Magnetic particles are disclosed as a preferable solid support, particularly 4.5 micron diameter DYNABEADS® (page 7 and pages 46-47, Example 15). Both the detection and separation reagents comprise monoclonal antibodies which specifically bind to surface antigens of the cells, some of the benefits of which are disclosed (pages 1a-2). For the separation reagent, the monoclonal antibodies

are covalently bound or physically adsorbed onto the surface of the solid support (Page 7). The method is taught as an alternative to "flux" (i.e flow) cytometry (e.g. pages 2-3).

Hajek et al (US 5,340,719) teach a method to identify characteristics expressed by formed bodies or cells, such as cell membrane molecules on those cells in or from a blood sample (e.g. column 5, lines 32-50), wherein the formed bodies or cells are combined with at least one set of microspheres, such as polystyrene latex microspheres (e.g. column 8, lines 42-48), having a reactant, such as antibody (column 3, lines 25-30), bound thereto (i.e. coated thereon), and specific binding between the formed bodies or cells and the coated microspheres is determined (e.g. columns 3-4). The reactant coated on the microspheres will bind to a specific molecule on the formed bodies or cells or, either simultaneously or sequentially, to a specific reactant which has bound to the molecule of interest on the formed bodies or cells (e.g. column 4, lines 26-44). In the fast cell screening embodiment of the method, agglutination of the formed bodies or cells with the coated microspheres is observed visually or optically (e.g.: column 4, lines 20-26; column 12). The reference exemplifies the agglutination of platelets with a particular antibody coated microsphere population (e.g. column 10, lines 26-30). The optical methods of the reference are taught as an alternative to flow cytometry (e.g. columns 1-3).

Harlow et al teach the conventional method of the detection of antigen-antibody binding by agglutination of antibody coated beads after the interaction of said beads with multivalent antigen (page 612) and teach common solid-phase supports for immunoassays including polystyrene beads which bind proteins in a nonspecific, noncovalent fashion so that after coating with antibody it is

required that the remaining binding sites be blocked to prevent further protein binding (pages 605 and 608).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted particle-based detection methods, such as fluorescent particle label methods, as taught by Margel et al, sandwich methods, as taught by Carriere, agglutination methods, as taught by Hajek et al or Harlow et al, or the microscopic method of Hajek et al, in the method of Abrams et al because: the coating of reactants such as antibodies onto particles such as polystyrene beads is conventional in the art; fluorescent particle labels are conventional in the art (Margel et al); sandwich methods using solid-phase immobilized separation reagent to detect cell-bound antigens are known and conventional in the art (Carriere); and, agglutination of reactant coated beads after interaction with multivalent binding pair members (Hajek et al or Harlow et al), including cell membrane molecules of blood formed bodies or cells as in Hajek et al, or staining of complexes between reactant coated beads and formed bodies or cells as in Hajek et al, allow for the simple visual or microscopic detection of binding pair complex formation. One would have had obvious motivation to use the method as modified by Margel et al because one would have reasonably expected a conventional particulate label to perform the desired labelling function in the method. One would have had obvious motivation to use the method as modified by Hajek et al and/or Harlow et al, or by Carriere, because either of Carriere or Hajek et al teach their methods as an alternative to the expensive and technically demanding method of flow cytometry. It would have been obvious to optimize the concentration of binding reactant for coating on the particles because such optimization

is routine and conventional in the art. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to have indirectly bound specific binding reactant such as antibody to the particle surface, either simultaneously or sequentially relative to binding pair interaction, with a specific binding reactant for the reactant such as anti-immunoglobulin or protein A or a biotin-avidin/streptavidin bridge in the method of Abrams et al, as modified, because, as taught in any of Abrams et al, Carriere, Hajek et al, or Margel et al, such indirect binding is conventional in the art as an alternative to direct binding. It would have been obvious to formulate the reagents of Abrams et al, as modified, into a kit since that is conventional in the art for convenience, economy, and reproducibility. It would have been further obvious to one of ordinary skill in the art at the time the instant invention was made to have provided anti-phosphatidylserine antibodies, as taught in Rote et al, for the methods of Abrams et al, as modified, for the detection of activated platelets and platelet-derived microparticles because Abrams et al teach re-orientation of phosphatidylserine in activated platelet membranes as an activation-dependent marker and Rote et al specifically teach antibodies which function for the detection thereof. One would have expected success in view of the successful use of the antibodies in Rote et al for the detection of platelet activation.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al in view of Rote et al and Margel et al as applied to claims 36-38 and 41 above, and further in view of Dachary-Prigent et al (Blood 81: 2554-2565, 15 May 1993).

Claims 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al in view of Rote et al and Carriere as applied to claims 36-38 and 41 above, and further in view of Dachary-Prigent et al (Blood 81: 2554-2565, 15 May 1993).

Claims 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abrams et al, in view of Rote et al, Hajek et al ('719), and/or Harlow et al, as applied to claims 36-38 and 41 above, and further in view of Dachary-Prigent et al (Blood 81: 2554-2565, 15 May 1993).

Although Abrams et al, as modified above, teach re-orientation of phosphatidylserine in activated platelet membranes as an activation-dependent marker, in contrast to the invention as instantly claimed the reference, as modified, does not teach annexin V as a probe for this activation-dependent marker.

Dachary-Prigent et al teach annexin V, a receptor for phospholipids, as a probe, in the presence of sufficient calcium, for activated platelets and platelet-derived microparticles and teach its use as an alternative to the antibody probes taught by, among others, Abrams et al (reference 12 of the publication).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted annexin V for the activation-specific antibody probes of Abrams et al, as modified, in view of the express suggestion in Dachary-Prigent et al to make such substitution.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

King teaches double rosette assays for the simultaneous detection of two cell-surface epitopes on the same particulate analyte using two different particles each coated with a different antibody, including monoclonal antibodies (entire document, particularly page 481, Abstract, pages 484-5, and page 486, Figure 2). The method is taught as an alternative to flow cytometry. As exemplified, one of the detection reagents was a fluorescently labelled particle of 0.7 microns diameter (bottom of page 483) directly coated with antibodies specific for one of the target epitopes, and the other detection reagent utilized an antibody sandwich comprising a soluble target-epitope specific antibody and an insolubilized anti-immunoglobulin for the detection of the antibody-bound target epitope. Either detection reagent could also function as a separation reagent, when bound, as rosettes were separated from unrosetted cells by density gradient centrifugation (paragraph bridging pages 481-2; page 484).

Goding teaches that the use of solid-phase immobilized cells is conventional in the art for determination of antibodies binding thereto (see pages 75-79).

Hemker et al (US 5,266,462) teach enzymatic determination of platelet procoagulant activity.

Connor et al (Proc. Natl. Acad. Sci. USA 86: 3184-3188, 1989) reacted adherent activated macrophages, inherently comprising receptors recognizing phosphatidylserine (PS), with procoagulant cells (i.e. MELC cells, see page 3185, column 1, page 3186, column 2, and page 3187, Table 1) and determined the binding of the procoagulant cells thereto, inherently via cell surface PS, after washing the solid phase to remove unbound components. The macrophage receptors are considered herein as indirectly bound to the solid phase via the adherent macrophages. Although the reference also teaches the prothrombin-converting activity assay for determination of surface PS, it does not teach immobilization of the cells for the determination.

Koopman et al (Blood 84:1415-1420, Sept 1994) teach annexin V for the determination of apoptotic cells.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to James L. Grun, Ph.D., Technology Center 1600, Group 1640, Art Unit 1641, whose telephone number is (703) 308-3980. The Examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Long Le, SPE, can be contacted at (703) 305-3399. The fax phone numbers for official communications to Group 1640 are (703) 305-3014 or (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

James L. Grun, Ph.D.
February 24, 2001

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641